Effect of Cardiac Resynchronization Therapy on Thyroid Function

Umut Celikyurt, MD; Aysen Agacdiken, MD; Bilal Geyik, MD; Guliz Kozdag, MD; Ahmet Vural, MD; Dilek Ural, MD

Department of Cardiology (Celikyurt, Agacdiken, Kozdag, Vural, Ural), Kocaeli University Medical Faculty, Kocaeli, Turkey; Department of Cardiology (Geyik), Trakya University Medical Faculty, Edirne, Turkey

ABSTRACT

Background: Heart failure patients frequently have thyroid function abnormalities. Cardiac resynchronization therapy (CRT) is a major treatment for patients with advanced chronic heart failure. We aimed to investigate the effects of CRT on thyroid functions.

Hypothesis: CRT improves thyroid functions.

Methods: Fifty-seven patients (42 male, 15 female; mean age 58 ± 13 y) undergoing CRT were included in the study. Serum levels of thyroid hormones and echocardiographic parameters were measured before and 6 months after CRT. A response to CRT was defined as a reverse remodeling detected by a relative increase of $\geq 15\%$ in left ventricular ejection fraction.

Results: The clinical status and functional capacity of the patients in the remodeling group were improved significantly. The mean New York Heart Association class was reduced from 3.2 ± 0.4 to 2.2 ± 0.4 ($P < 0.001$). The free triiodothyronine (fT₃) level increased from 2.67 pg/mL to 2.97 pg/mL in the reverse remodeling group ($P = 0.005$). The fT₃/fT₄ ratio increased from 1.81 to 2.34 ($P = 0.006$).

Conclusions: CRT improves fT₃ levels and fT₃/fT₄ ratio, which may play an important role in reverse remodeling.

Introduction

Cardiac resynchronization therapy (CRT) is a major treatment for patients with advanced chronic heart failure (HF) and prolonged QRS complex duration. CRT has been demonstrated to improve HF symptoms, improve quality of life, and reduce HF hospitalization rates and mortality.¹

Thyroid hormone (TH) plays an important role in cardiovascular homeostasis. TH influences cardiac contractility, heart rate, diastolic function, and systemic vascular resistance. Studies demonstrated that approximately 30% of patients with congestive HF have low T₃ levels. Reduced T₃ is associated with the severity of the HF and is a predictor of cardiovascular and all-cause mortality.^{2,3} However, changes in thyroid functions after CRT have not been investigated. The aim of this study was to investigate the effects of CRT on thyroid functions.

Methods

Patients

Fifty-seven patients (42 male, 15 female; mean age 58 ± 13 y) undergoing CRT were included in the study. Patients were selected according to the following criteria:¹ chronic HF (New York Heart Association [NYHA] class III

or IV),² wide QRS interval,³ and left ventricular ejection fraction (LVEF) $\leq 35\%$. All patients were in sinus rhythm and receiving optimal medical therapy for HF. Exclusion criteria were presence of any concomitant systemic disease, hyper- or hypothyroidism, therapy with amiodarone, thyroid hormones, dopamine, steroids, or heparin. Written informed consent was obtained from all patients. The study was approved by the local ethics committee.

Cardiac Resynchronization Therapy Device Implantation

All pacemaker implantations were performed by left infraclavicular approach. Right atrial and right ventricular leads were implanted using a transvenous approach. Left ventricular (LV) leads were inserted by a transvenous approach through the coronary sinus into a cardiac vein of the free wall.

Patients received a biventricular pacemaker (InSync III; Medtronic Inc., Minneapolis, MN) or a biventricular cardioverter-defibrillator (InSync ICD; Medtronic Inc.). The atrioventricular interval was optimized using Doppler echocardiography after 1 week of implantation.

Echocardiography

Patients were imaged in the left lateral decubitus position with a commercially available system (VIVID 7; General Electric-Vingmed Ultrasound, Horten, Norway). Images were obtained with a 2.5-MHz broadband transducer at a

The authors have no funding, financial relationships, or conflicts of interest to disclose.

depth of 16 cm in the parasternal and apical views (standard long-axis, 2- and 4-chamber images). Standard 2-dimensional and color Doppler data triggered to the QRS complex were saved in cine loop format. LV volumes were calculated using the Teichholz method, and LVEF was calculated from the conventional apical 2- and 4-chamber images using the biplane Simpson's technique.⁴ A response to CRT was defined as a reverse remodeling detected by a relative increase of $\geq 15\%$ in LVEF.

Transthoracic echocardiography was performed 1 week before pacemaker implantation and repeated 6 months later. All echocardiographic measurements after CRT implantation were made with the device in active pacing mode.

Blood Samples

Fasting blood samples were drawn from a large antecubital vein. The samples were centrifuged for 10 minutes and serum free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) levels were determined by the Immulite 2000 (Bio DPC, Los Angeles, CA) at baseline and 6 months later. The reference intervals of our laboratory are as follows: TSH 0.4–4 $\mu\text{IU/mL}$, fT3 1.57–4.71 pg/mL, fT4 0.8–1.9 ng/dL.

Statistical Analysis

All analyses were performed with the statistical software program SPSS version 13.0 (SPSS, Inc., Chicago, IL). Continuous data were expressed as mean (standard deviation). A comparison of the clinical echocardiographic variables and thyroid function tests before and after CRT was performed by paired sample *t* test or Wilcoxon signed rank test. The Mann-Whitney *U* test was used to assess differences in baseline thyroid hormone levels between the reverse remodeling and no remodeling groups. A value of $P < 0.05$ was considered statistically significant.

Results

The study population consisted of 57 patients. Baseline characteristics of the study group are shown in Table 1. Reverse remodeling was developed in 48 (84%) patients. Reverse remodeling did not occur in 9 (16%) patients. The clinical status and functional capacity of the patients in the remodeling group were improved significantly. The mean NYHA class was reduced from 3.2 ± 0.4 to 2.2 ± 0.4 ($P < 0.001$). The mean NYHA functional class was not improved in the no remodeling group.

The baseline TSH, fT3, and fT4 levels for reverse remodeling and no remodeling groups showed no statistically significant difference ($P > 0.05$). The fT3 level increased from 2.67 pg/mL to 2.97 pg/mL in the reverse remodeling group ($P = 0.005$). The fT3/fT4 ratio increased from 1.81 to 2.34 ($P = 0.006$) (Table 2). There was no significant relationship between fT3 levels and fT3/fT4 ratio in the no remodeling group. The range of TSH, fT3, and fT4 levels in the no remodeling group were 0.6–3.24, 1.83–3.38, and 1–1.75, respectively. The fT3 level and fT3/fT4 ratio decreased from 2.58 pg/mL to 2.41 pg/mL and 1.83 to 1.59 in the no remodeling group, respectively (Table 3).

Table 1. Patient Characteristics

	Remodeling Group (n = 48)	No Remodeling Group (n = 9)
Age (y)	58 $\pm$ 13	57 $\pm$ 11
Men, no. (%)	33 (69)	6 (67)
Etiology		
Nonischemic, no. (%)	38 (79)	3 (33)
Ischemic, no. (%)	10 (21)	6 (67)
Hypertension, no. (%)	37 (77)	6 (67)
Diabetes, no. (%)	17 (35)	4 (44)
NYHA (mean)	3.2 $\pm$ 0.4	3.1 $\pm$ 0.6
LVEF (%)	22.6 $\pm$ 5	21.8 $\pm$ 4
Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.		

Table 2. Baseline and 6-Month Values in Reverse Remodeling Group (n = 48)

	Baseline	6 Months	P
fT3	2.67 $\pm$ 0.7	2.97 $\pm$ 0.5	<0.05
fT4	1.54 $\pm$ 0.3	1.32 $\pm$ 0.3	<0.05
TSH	1.27 $\pm$ 0.8	1.82 $\pm$ 1.2	<0.05
fT3/fT4	1.81 $\pm$ 0.5	2.34 $\pm$ 0.6	<0.05
Abbreviations: fT3, free triiodothyronine; fT4, free thyroxine; fT3/fT4, free triiodothyronine/free thyroxine ratio; TSH, thyroid-stimulating hormone.			

Table 3. Baseline and 6-Month Values in No Remodeling Group (n = 9)

	Baseline	6 Months	P
fT3	2.58 $\pm$ 0.5	2.41 $\pm$ 0.5	>0.05
fT4	1.43 $\pm$ 0.2	1.57 $\pm$ 0.4	>0.05
TSH	1.7 $\pm$ 0.8	2.07 $\pm$ 1.4	>0.05
fT3/fT4	1.83 $\pm$ 0.4	1.59 $\pm$ 0.5	>0.05
Abbreviations: fT3, free triiodothyronine; fT4, free thyroxine; fT3/fT4, free triiodothyronine/free thyroxine ratio; TSH, thyroid-stimulating hormone.			

Discussion

Low fT3 levels were associated with cardiac mortality and poor short-term survival in congestive HF. The enzyme 5'-mono-deiodinase is responsible for converting T4 to T3 in peripheral tissue.^{5–7} The activity of the enzyme is reduced in chronic illnesses and congestive HF. Reduced renal blood flow, poor nutritional status, liver congestion, and peripheral metabolic changes were associated with low T3 levels.^{7–9} Studies also showed that low fT3 levels were associated with larger heart chambers and worse LV systolic ejection fraction.⁷ Kozdag et al reported that low fT3/fT4 ratio is

significantly associated with an advanced disease status, reduced LVEF, and severe mitral regurgitation.⁷

Our study demonstrated that fT3 levels and fT3/fT4 ratio were significantly increased in the reverse remodeling group. The improved hemodynamic parameters with CRT has been reported in previous studies.^{10,11} The increased fT3 levels and fT3/fT4 ratio in the reverse remodeling group may be related to improved LVEF and renal blood flow, and reduced liver congestion after CRT. We have detected increased TSH concentration in the remodeling group. This may relate to the improvement of ejection fraction. Ejection fraction was significantly correlated with serum TSH concentration in a study of patients with compensated CHF.¹²

Silva-Tinoco et al recently demonstrated the development of thyroid function disorders in HF patients on conventional treatment in a 6-month follow-up period.¹³ In our study, fT3 levels and fT3/fT4 ratio were decreased in the no remodeling group without any development of hypothyroidism or low T3 syndrome. Absence of development of any thyroid function disorder in both the reverse remodeling and no remodeling groups in a similar follow-up period may relate to the beneficial effects of CRT on hemodynamic parameters besides effects of CRT on cardiac function.

Forini et al showed that decreased T3 levels in the long term resulted in cellular and structural impairment, which resemble the changes observed during HF progression.¹⁴ Low T3 levels may contribute to the HF process and may play a role in the remodeling of the LV. It has been shown that TH treatment after myocardial infarction resulted in favorable changes in left ventricular geometry.¹⁵ TH normalizes wall stress by increasing cardiac mass and prevents spherical shape development of the left ventricle chamber, which can result in improvement of myocardial performance.^{15,16} In our study, the increased T3 levels in the remodeling group may contribute to the reverse remodeling process, and probably has an important role in reverse remodeling development.

Conclusion

CRT improves fT3 levels and fT3/fT4 ratio in the reverse remodeling group and may prevent development of thyroid function disorder in HF patients even in the absence of reverse remodeling. Further studies are needed to confirm our findings.

Limitations

One limitation of our study was the relatively small sample size. Another limitation was that longer follow-up might be

required to better evaluate the effect of CRT on thyroid function. In addition, our results cannot be extended to all patients with CRT because we excluded HF patients with hyper- or hypothyroidism.

References

1. Landolina M, Lunati M, Gasparini M, et al. Comparison of the effects of cardiac resynchronization therapy in patients with class II versus class III and IV heart failure (from the InSync/InSync ICD Italian Registry). *Am J Cardiol*. 2007;100:1007–1012.
2. Klein I, Danzi S. Thyroid disease and the heart. *Circulation*. 2007;116:1725–1735.
3. Iervasi G, Pingitore A, Landi P, et al. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. *Circulation*. 2003;107:708–713.
4. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2:358–367.
5. Utiger RD. Altered thyroid function in nonthyroidal illness and surgery. To treat or not to treat? *N Engl J Med*. 1995;333:1562–1563.
6. Chopra IJ. Clinical review 86: Euthyroid sick syndrome: is it a misnomer? *J Clin Endocrinol Metab*. 1997;82:329–334.
7. Kozdag G, Ural D, Vural A, et al. Relation between free triiodothyronine/free thyroxine ratio, echocardiographic parameters and mortality in dilated cardiomyopathy. *Eur J Heart Fail*. 2005;7:113–118.
8. Kimura T, Kanda T, Kotajima N, et al. Involvement of circulating interleukin-6 and its receptor in the development of euthyroid sick syndrome in patients with acute myocardial infarction. *Eur J Endocrinol*. 2000;143:179–184.
9. Girvent M, Maestro S, Hernandez R, et al. Euthyroid sick syndrome, associated endocrine abnormalities, and outcome in elderly patients undergoing emergency operation. *Surgery*. 1998;123:560–567.
10. Bhatia V, Bhatia R, Dhindsa S, et al. Cardiac resynchronization therapy in heart failure: recent advances and new insights. *Indian Pacing Electrophysiol J*. 2006;3:129–142.
11. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the Multisite STimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol*. 2002;40:111–118.
12. Calvo-Romero JM, Rodriguez EM. Serum-free thyroxine and thyrotropin concentrations in euthyroid patients with decompensated congestive heart failure. *Int J Cardiol*. 2005;102:367–368.
13. Silva-Tinoco R, Castillo-Martinez L, Orea-Tejeda A, et al. Developing thyroid disorders is associated with poor prognosis factors in patient with stable chronic heart failure. *Int J Cardiol*. 2011;147:e24–e25.
14. Forini F, Paolicchi A, Pizzorusso T, et al. 3,5,3'-Triiodothyronine deprivation affects phenotype and intracellular [Ca²⁺]_i of human cardiomyocytes in culture. *Cardiovasc Res*. 2001;51:322–330.
15. Pantos C, Mourouzis I, Cokkinos DV. New insights into the role of thyroid hormone in cardiac remodeling: time to reconsider? *Heart Fail Rev*. 2011;16:79–96.
16. Pantos C, Mourouzis I, Markakis K, et al. Thyroid hormone attenuates cardiac remodeling and improves hemodynamics early after acute myocardial infarction in rats. *Eur J Cardiothorac Surg*. 2007;2:333–339.